Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8811

Kurt R. Nielsen, Ph.D.
Executive Director, Generic R&D

Direct Dial: (215) 591 8716
Direct Fax: (215) 591 8811
kurt.nielsen@tevausa.com

JAN 15 2004

CONFIDENTIAL

January 6, 2004

VIA CERTIFIED MAIL- RETURN RECEIPT REQUESTED:

President
G.D. Searle LLC
4901 Searle Parkway
Skokie, IL 60077
(As NDA owner)

President
Pharmacia Corporation
4901 Searle Parkway
Skokie, IL 60077

President
Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017-5755

President
G.D. Searle & Co.
c/o Corporate Patent Department
P.O. Box 5110
Chicago, IL 60680
(As owner of U.S. Patent 5,760,068)

President
G.D. Searle & Co.
c/o Corporate Patent Department
5200 Old Orchard Road
Skokie, IL 60077
(As owner of U.S. Patents 5,466,823 & 5,563,165)

Re: Patent Certification Notice
U.S. Patent Nos. 5,466,823, 5,563,165 and 5,760,068
Celecoxib Capsules, 100 mg, 200 mg and 400 mg
Teva Pharmaceuticals USA, Inc.'s ANDA 76-898

To Whom It May Concern:

The purpose of this communication is to provide the notice and information required by 21 U.S.C. § 355(j)(2)(B)(i) and (ii) (sections 505(j)(2)(B)(i) and (ii) of the Food, Drug and Cosmetic Act) that Teva Pharmaceuticals USA, Inc. ("Teva"), a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania, has submitted an ANDA for this drug product which contains the required bioavailability and/or bioequivalence data and Paragraph IV certifications with respect to U.S. Patent Nos. 5,466,823 ("the '823 patent"), 5,563,165 ("the '165 patent") and 5,760,068 ("the '068 patent").

A detailed statement of the factual and legal bases for Teva's position regarding the '823,

'165 and '068 patents is provided herein. Teva reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patents are invalid, unenforceable, or will not be infringed.

Sincerely,

Kurt Nielsen, Ph.D.
Executive Director, Generic R&D

Enclosure: Teva Pharmaceuticals USA, Inc.'s Detailed Statement Of The Factual And Legal Bases That U.S. Patents 5,466,823, 5,563,165 and 5,760,068 Are Invalid, Unenforceable, Or Not Infringed

This is the detailed statement of Teva Pharmaceuticals USA, Inc. ("Teva"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c), of the factual and legal bases why U.S. Patent Nos. 5,466,823 ("the '823 patent"), 5,563,165 ("the '165 patent") and 5,760,068 ("the '068 patent") are invalid, unenforceable, or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use, sale or offer for sale in the United States, or importation into the United States, of Teva's 100 mg, 200 mg and 400 mg celecoxib capsules ("Teva's products"), for which this detailed statement is submitted. Teva's bases follow.

I. THE PATENTS

A. U.S. Patent No. 5,466,823

The '823 patent contains 13 claims, of which claims 1 and 7 are independent. Claims 1 and 7 each recite a large genus of compounds, one member of which is celecoxib.

Claims 2-6 depend from claim 1 and set forth narrower sub-genera of compounds. Claims 4-6 limit the members of the genus such that they exclude celecoxib.

Claims 8-13 depend from claim 7 and provide further limitations to the R^2 substituent (claim 8), and set forth specific compounds of the genus. Claims 10 and 12 recite specific compounds that are not celecoxib.

B. U.S. Patent No. 5,563,165

The '165 patent contains 21 claims, of which claims 1 and 15 are independent claims. Claims 1 and 15 recite pharmaceutical compositions comprising a therapeutically effective amount of a compound selected from a large genus of compounds.

Claims 2-14 depend, directly or indirectly, from claim 1 and add additional limitations to the genus from which the therapeutically effective amount of compound is selected. Claims 6-14 narrow this genus such that it does not include celecoxib.

Claims 16-21 depend, directly or indirectly, from claim 15 and add additional limitations to the genus from which the therapeutically effective amount of compound is selected. Claims 19-21 narrow this genus such that it does not include celecoxib.

C. U.S. Patent No. 5,760,068

The '068 patent contains 18 claims, of which claims 1, 6, 9 and 11 are independent.

Independent claims 1, 6, 9 and 11 are directed to methods of treatment involving administration of a compound selected from a large genus of compounds (which differs depending on the claim). The compounds recited in independent claim 6 and the claims

depending therefrom (claims 7-8) do not include celecoxib. Claim 9 and claim 10, which depends therefrom, also do not include celecoxib.

The claims that depend, directly or indirectly, from claims 1 and 11 further limit the genus of compounds recited in the independent claim from which they respectively depend. Claim 5 limits the genus of compounds such that it no longer includes celecoxib.

Claim 18 claims the method of claim 1 "for use in the prevention of colorectal cancer."

II. LEGAL PRINCIPLES

A. Non-Infringement

A person is a direct infringer under 35 U.S.C. § 271(a) if that person makes, uses, sells or offers to sell in the United States, or imports into the United States, any patented invention without authorization of the patent holder. Direct infringement may be either literal or under the doctrine of the equivalents.

1. Literal Infringement

Literal infringement of a patent claim requires that the accused device contain each and every limitation recited in the claim. *See Carroll Touch, Inc. v. Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1579 (Fed. Cir. 1993). If there is any deviation or if any limitation is missing, there can be no literal infringement as a matter of law. *Lantech, Inc. v. Keip Mach. Co.*, 32 F.3d 542 (Fed. Cir. 1994).

2. Infringement Under the Doctrine of Equivalents

Under the doctrine of equivalents, "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17, (1997). If the difference is substantial, there would be no infringement under the doctrine. *See Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512 (Fed. Cir. 1995) (*en banc*), *rev'd on other grounds*, 520 U.S. 17 (1997).

The doctrine of equivalents may not be used to embrace a structure that is specifically excluded from the scope of the claims. *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1582 (Fed. Cir. 1996). In addition, the doctrine may not be used to expand the scope of a patentee's right to exclude so as to encompass the prior art. *Dawn Equip. Co. v. Kentucky Farms, Inc.*, 140 F.3d 1009, 1017 (Fed. Cir. 1998); *General Am. Transportation Corp. v. Cryo-Trans, Inc.*, 93 F.3d 766, 771 (Fed. Cir. 1996).

3. Determination of Infringement

To determine whether a product infringes a United States patent, there is a two-step inquiry in which the court: (1) construes the claim; and (2) compares the properly construed claim to the accused device or process. *Carroll Touch, Inc. v. Electro Mechanical Sys., Inc.*, 15 F.3d 1573, 1576 (Fed. Cir. 1993).

When construing a claim the courts should rely on the claim language, the specification, the prosecution history, and if necessary to aid the court's understanding of the patent, extrinsic evidence. *See Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302 (Fed. Cir. 2000); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1500 (Fed. Cir. 1998). The doctrine of claim differentiation is a guide to claim construction whereby the limitations of one claim should not be interpreted so as to make another claim (such as a dependent claim) identical in scope.

Once a claim has been construed, the properly construed claim is then compared to the accused device (or process) to determine if there is infringement.

B. Invalidity

1. Anticipation

A claimed invention is invalid as anticipated if it was described in a patent or printed publication either before the date of invention by the applicant or more than one year before the filing date of the application. 35 U.S.C. §§ 102(a), (b). A patent or printed publication anticipates a claimed invention if it expressly describes the claimed invention, or if the claimed invention is necessarily inherent in the patent or printed disclosure. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1346-47 (Fed. Cir. 1999); *Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 1007 (1988); *Verdegaal Brothers, Inc. v. Union Oil Co.*, 814 F.2d 628, 633 (Fed. Cir.), *cert. denied*, 484 U.S. 827 (1987); *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986); *Hughes Aircraft Co. v. United States*, 8 U.S.P.Q.2d 1580, 1583 (Ct. Cl. 1988), *dismissed in part, aff'd in part without op'n.*, 862 F.2d 320 (Fed. Cir. 1988).

2. Obviousness

A claim is invalid if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. § 103. This inquiry is a question of law based on factual inquiries. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

The test for obviousness set forth in *Graham* is a four part inquiry which considers: scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art, and evidence of secondary considerations, when such

evidence is present. *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984).

Such secondary considerations include unexpected results, commercial success of the invention, whether the invention solved a long felt need, copying of the invention by others in the field, and failure of others to solve the problem that the inventor solved. For a claimed invention's commercial success to be given substantial weight, a nexus must be established between the merits of the claimed invention and the commercial success. *Cable Electric Products Inc. v. Genmark, Inc.*, 770 F.2d. 1015, 1027 (Fed. Cir. 1985). The patentee bears the burden of establishing a *prima facie* case of such a nexus. *Demaco Corp. v. F. Von Langsdorf Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988).

The objective indicia or "secondary considerations" of nonobviousness, however, do not control the analysis when there is an otherwise strong case of obviousness, such as one based upon prior art not considered by the Patent and Trademark Office during prosecution. *Newell Companies, Inc. v. Kenny Mfg. Co.*, 864 F.2d 757, 768-769 (Fed. Cir. 1988).

A claim may be proven obvious in view of a single prior art reference or in view of a combination of prior art references. When prior art references are combined to invalidate a claim under 35 U.S.C. § 103, some teaching, suggestion or motivation to combine the references must exist that is found in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). An absolute prospect for success is not required for a finding of obviousness; rather, only a reasonable expectation is needed. *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988).

3. Written Description and Enablement Requirements

The first paragraph of 35 U.S.C. § 112 sets forth, *inter alia*, the written description and enablement requirements for a valid patent:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

To comply with § 112, first paragraph, the claims of a patent must be adequately supported by the written description of the invention set forth in the patent specification. *See Reiffen v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). To satisfy the written description requirement, the applicant must convey with reasonable clarity to those of skill in the art that, as of the filing date, the applicant was "in possession" of the claimed invention. *Purdue Pharma L.P. v Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); *Fiers v. Revel*, 984 F.2d 1164, 1170 (Fed. Cir. 1993). To do so, the specification must "describe an invention and do so

in sufficient detail that one skilled in the art can clearly conclude that the 'inventor invented the claimed invention.'" *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1556, 1559 (Fed. Cir. 1997). The disclosure need not parrot the language of the claims, but "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma.*, 230 F.3d at 1323 (citations omitted).

With respect to enablement, the Federal Circuit has stated: "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)); *see also In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). "In cases involving unpredictable factors, such as most chemical reactions ..., the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Bowen*, 492 F.2d 859, 862 (C.C.P.A. 1974). *See also In re Fisher* 427 F.2d 833, 839 (C.C.P.A. 1970), *In re Vaeck* 947 F.2d 488, 496 (Fed. Cir. 1991). Whether claims are sufficiently enabled by the specification is determined as of the filing date of the patent application. *Enzo Biochem, Inc. v. Calgene Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

The specification must support the full scope of the patent claims and must "'describ[e] the invention, *with all its claimed limitations* . . .'" *Eli Lilly*, 199 F.3d at 1566; *see Fiers*, 984 F.2d at 1170 ("An adequate description of a DNA requires more than a mere statement that it is part of the invention and a potential method for isolating it; what is required is a description of the DNA itself."). Thus, even if the specification enables one skilled in the art to make and use the invention, it may still fail to meet the written description requirement of § 112, first paragraph. *See Vas-Cath, Inc. v Mahurkar*, 935 F.2d 1555, 1561-62 (Fed. Cir. 1991).

C. Inequitable Conduct

A duty of candor exists for all individuals involved in the prosecution of a U.S. patent application. Specifically, 37 C.F.R. § 1.56 states, in pertinent part:

> . . . Each individual associated with the filing and prosecution of a patent application has a duty of good faith and candor . . . to disclose to the Office all information known to that individual to be material to patentability . . . .

37 C.F.R. § 1.56 (July 1997).

Information is deemed material if there "is a 'substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent'". *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1327 (Fed. Cir. 1998) (citations omitted). For instance, information about copending patent applications may be material. Information relevant to determining inventorship issues is also material. *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1321 (Fed. Cir. 2000) (citations omitted).

Inequitable conduct includes affirmative misrepresentations of material fact, failure to disclose material information, or submission of false material information, together with an intent to deceive. *See Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178-1179 (Fed. Cir. 1995). A breach of a party's duty under 37 C.F.R. § 1.56 may constitute inequitable conduct, thereby rendering the patent unenforceable. *Elk Corp. of Dallas v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed. Cir. 1999).

The inquiry into whether there is inequitable conduct requires a two-step analysis: (1) the conduct must meet a threshold level of materiality; and (2) the evidence must show a threshold level of intent to mislead the PTO. *PerSeptive*, 225 F.3d at 1319. The more material the omission, the less intent need be inferred. *Id.* Generally, a finding of inequitable conduct "hinges on whether the evidence as a whole indicates that the patentees or their representatives acted with the intent to deceive." *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1381 (Fed. Cir. 2001).

The Federal Circuit has stated that "intent" commonly means:

> Design, resolve, or determination with which [a] person acts[; a] state of mind in which a person seeks to accomplish a given result through a course of action.

Molins, 48 F.3d 1172 at 1180 (citations omitted). Intent does not have to be proven by direct evidence but can be inferred from the facts and circumstances surrounding the applicant's conduct. *Molins*, 48 F.3d 1172 at 1180-81. When there is a high level of materiality, the level of intent that needs to be shown can be proportionally less. *Brasseler*, 267 F.3d at 1381.

III. TEVA'S GENERIC CELECOXIB WILL NOT INFRINGE ANY VAILD/ENFORCEABLE CLAIM OF THE '823 PATENT

A. Teva's Generic Celecoxib Will Not Infringe Claims 4-6, 10 and 12 of the '823 Patent

Claims 4-6, 10 and 12 of the '823 patent are directed to a groups of compounds (or with respect to claim 10, a compound) that do not include celecoxib. Teva's generic celecoxib products will not contain any active pharmaceutical compound other than celecoxib. Therefore, Teva's celecoxib products do not literally infringe claims 4-6, 10 and 12 of the '823 patent.

Teva's celecoxib products also would not infringe these claims under the doctrine of equivalents because the '823 patent contains claims directed specifically to pharmaceutical compounds including celecoxib. Therefore, under the doctrine of claim differentiation, claims 4-6, 10 and 12 would not be construed so as to encompass Teva's generic celecoxib products. *Kraft Foods Inc. v. International Trading Co.*, 203 F.3d 1362 (Fed. Cir. 2000). Furthermore, it would make no sense to use the doctrine of equivalents to expand the scope of a claim to cover that which is already literally recited by another claim.

B. At Least Claims 1-3, 7-9, 11 and 13 of the '823 Patent Are Invalid Under 35 U.S.C. § 103

At least claims 1-3, 7-9, 11 and 13 of the '823 patent are invalid under 35 U.S.C. § 103 because they are obvious in view of Canadian Patent No. 1,130,808 to Micetich ("the '808 patent"), the El-Khawass article (Journal OF THE CHINESE CHEMICAL SOCIETY, 37, 605-609 (1990) ("the El-Khawass article"), U.S. Patent No. 3,427,305 to Chinn ("the '305 patent"), U.S. Patent No. 5,134,142 to Matsuo ("the '142 patent"), and/or U.S. Patent No. 5,051,518 to Murray ("the '518 patent").

The prosecution history does not show that applicants relied on any meaningful secondary consideration to obtain allowance of the '823 patent, nor are we aware of any such evidence arising from the merits of the subject matter of all the claims of the '823 patent. Any commercial success that Celebrex® has enjoyed is not substantially due to the claimed invention, but rather to Pfizer's preeminent position in the pharmaceutical industry, and the particular marketing strategy adopted for Celebrex®, including the apparent misrepresentation that Celebrex® is associated with lower risk of gastrointestinal complications than other NSAIDs. *See, e.g., Note of Caution: Study Raises Specter Of Cardiovascular Risk For Hot Arthritis Pills*, Wall Street Journal, August 22, 2001; Chan, Francis K.L. *et al.*, *Celecoxib Versus Diclofenac and Omeprazole in Reducing the Risk or Recurrent Ulcer Bleeding in Patients with Arthritis*, N. Engl. J. Med., Vol 347, No. 26, 2104-2110 (December 26, 2002) ("Chan *et al.*"); *and* Graham, David Y., *NSAIDs, Helicobacter Pylori, and Pandora's Box*, N. Engl. J. Med., Vol 347, No. 26, 2162-2164 (December 26, 2002).

Accordingly, no secondary considerations overcome the otherwise strong case of obviousness that exists in connection with the '165 patent claims.

C. Inequitable Conduct Renders All Claims of the '823 Patent Unenforceable

During the prosecution of the '823 patent, Searle breached its duty of candor under 37 C.F.R. § 1.56 by failing to disclose the '808 patent and material references cited in an International Search Report ("ISR") in a related application. Searle admitted knowledge of and tacitly conceded the materiality of the references cited in the ISR by submitting them in an IDS in the '165 patent, a divisional of the '823 patent. These references, which disclose compounds as opposed to compositions, are even more material to the compound claims of the '823 patent than to the pharmaceutical composition claims of the '165 patent. Applicants' failure to investigate the '808 patent and failure to cite material references cited in the ISR evidence an intent to deceive the PTO. For at least these reasons, the '823 patent should be held to be unenforceable because of inequitable conduct.

1. Searle Breached its Duty of Candor Under 37 C.F.R. § 1.56

a. The '808 Patent

The '823 patent was prosecuted by Mr. Joseph W. Bulock ("Bulock"), in-house patent counsel for Searle. Bulock filed the application that resulted in the '823 patent on November 30, 1993, for a class of substituted pyrazolyl benzenesolfonamide compounds for treating inflammation and inflammation-associated disorders. In the first information disclosure statement ("IDS") submitted during prosecution, Bulock disclosed U.S. Pat. No. 5,134,142 to Matsuo. Bulock characterized Matsuo as disclosing 1,5 diaryl pyrazoles having anti-inflammatory activity. Matsuo refers to the '808 patent in its disclosure, stating that "[s]ome pyrazole derivatives having antiinflammatory and analgesic activities have been known as described for example, in Canadian Patent 1 130 808 . . . ."

The '808 patent discloses the genus of compounds set forth in Formula I of the '823 patent, with R^1 being an alkyl, alkoxy, or halogen (*see* '808 patent, page 1, lines 1-13). The '808 patent thus anticipated or at least made obvious at least original claim 1 of the '823 patent, as filed. Accordingly, the '808 patent was material and should have been disclosed. Even after the claims of the '823 patent were amended, the '808 patent remained material because some of the pending claims of the '594 application would have been obvious over the '808 patent.

b. The Articles Cited in the ISR for the '720 PCT Application

The '720 PCT Application claims priority from the '823 patent. During prosecution of the '823 patent, Bulock violated his duty to disclose by failing to disclose material prior art cited in the ISR in the '720 PCT Application, which was mailed March 23, 1995 (approximately 8 months before the November 1995 issuance of the '823 patent). Specifically, the ISR listed 10 references with respect to the PCT Application (which disclosed and claimed similar compounds to the '823 patent). Of those 10 references, Bulock had submitted 4 in a January 11, 1994 IDS. Bullock never submitted the other 6 references to the Examiner.[1] The ISR designated these 6 references as "X" references, meaning that the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the reference is taken alone. The 6 undisclosed ISR references were directed to treatment of inflammation using a compound covered by the claims of the '823 patent.

On August 23, 1995, during prosecution of the '165 patent (a divisional of the '823 patent), Bulock submitted an IDS with the ISR references. In the IDS, Bulock specifically stated that these documents were believed to be material to the subject matter of the application. The

---

[1] These 6 references are (1) Mokhtar, H., *Synthesis of Nitrogenous Compounds, Part II*, PAK. J. SCI. IND. RES. 33:30 (1990); (2) Mokhtar, H., *Synthesis of Nitrogenous Compounds from δ-Unsaturated 1,3-Dicarbony Esters. Part I. Substituted Pyrazoles, Isoxazoles and Oxyquinoxalines*, J. CHEM. SOC. PAK. 10:414 (1988); (3) Soliman, R., *et al.*, *Synthesis and Antidiabetic Activity of Some Sulfonylurea Derivatives of 3,5-Disubstituted Pyrazoles*, J. Pharm. Sci. 72:999 (1983); (4) EP 554 829; (5) US 4,146,721; and (6)Makki, M.S.I., *et al.*, Chem. Abstracts, 121:11 1994).

claims of the '823 patent were compound claims while the claims of the '165 patent were composition claims utilizing the compounds claimed in the '823 patent. The alleged invention of the '165 patent thus entailed use of the compounds claimed in the '823 patent. Hence, if the ISR references were material to prosecution of the '165 patent, they would also be material to prosecution of the '823 patent. By failing to submit those six material references to the Examiner during prosecution of the '823 patent, Bulock breached his duty under 37 C.F.R. § 1.56.

Moreover, MPEP 2001.06(a) states that individuals as set forth in 37 C.F.R. §1.56 (such as Bulock) "have a duty to bring to the attention of the [Patent] Office any material prior art or other information cited or brought to their attention in any related foreign application. As set forth above, the six ISR references Bulock did not cite were material to prosecution of the '823 patent. These ISR references were brought to Bulock's attention in a related foreign application – the '720 PCT Application. Therefore, according to the MPEP, Bulock breached his duty of candor under 37 C.F.R. § 1.56 by failing to bring the six ISR references to the attention of the Examiner responsible for the '823 patent application.

2. Searle Had An Intent to Deceive

Searle's intent to deceive does not have to be proven by direct evidence. *Molins*, 48 F.3d at 1180-81. Intent can be inferred from the facts and circumstances surrounding Bulock's conduct. *Id.* Here, the facts establish a strong inference of Searle's intent to deceive.

a. The '808 Patent

As discussed above, Bulock submitted Matsuo as a material reference, and therefore must have reviewed Matsuo, at least to evaluate its materiality, prior to its submission. Thus, Bulock would have also have known about the '808 patent as cited in Matsuo. In view of Bulock's characterization of Matsuo as disclosing 1,5 diaryl pyrazoles having anti-inflammatory activity, and Matsuo's statement that other pyrazole derivatives, such as those described in the '808 patent, have anti-inflammatory activities, Bulock should reasonably have investigated the '808 patent. *Brasseler*, 267 F.3d at 1383. Had Bulock done so, he would have brought the '808 patent to the attention of the Examiner because the '808 patent is clearly a material non-cumulative reference. Bulock's inaction evidences Bulock's intent to withhold the reference.

b. Bulock Did Not Submit Articles Cited in the International Search Report

The 6 ISR references cited in the '165 patent, but not the '823 patent, generally relate to pyrazoles. Some of the references specifically related to the use of pyrazoles to treat inflammation and others relate to treatment of hypoglycemia. Claims in the '823 patent and '720 PCT Application overlapped in subject matter during the pendency of the '823 patent application. Therefore, with respect to the '823 patent, the ISR references are highly material references.

Moreover, Bulock specifically cited these references as material during the prosecution of the '165 patent – a composition patent utilizing the compounds of the '823 patent. Yet he failed to cite the references in the parent '823 application that actually claimed pyrazole compounds.

Given the close relationship of the '823 patent and its divisional, the '165 patent, and given the high materiality of the ISR references (which were cited in the ISR with respect to claims that directly overlap claims in the '823 patent), less intent must be shown. *Brasseler*, 267 F.3d at 1381. Failure to cite these references evidences that Bulock withheld these references from the '823 patent with an intent to deceive.

c. Bulock Did Not Submit The References Even Though There Was Ample Time To Do So

There was ample time for Bulock to file the additional references during prosecution of the '823 patent. The ISR was mailed on March 23, 1995, almost 8 months before the '823 patent issued. On August 23, 1995, almost 3 months before the '823 patent issued, Bulock submitted an IDS for the '165 patent including the 6 ISR references. Thus, Bulock had more than sufficient time to submit the ISR references during prosecution of the '823 patent. Bulock's failure to submit these references further evidences his intent to withhold material information from the PTO during the '823 patent prosecution.

3. Searle Engaged in Inequitable Conduct

Given the materiality of the '808 patent, the high materiality of the 6 ISR references cited in the '165 patent and '720 PCT Application, and ample time Bulock had to submit the ISR references during prosecution of the '823 patent, the level of intent that needs to be shown can be proportionally less. *Brasseler*, 267 F.3d at 1381. Viewing the "evidence as a whole" indicates that Bulock knew that references existed that disclosed compounds similar to those claimed in the '823 patent and that he intended to withhold those material references from the PTO during prosecution of the '823 patent. Given the materiality of the uncited ISR references and the inference of intent, Bulock's inaction rises to the level of inequitable conduct sufficient to render the '823 patent unenforceable.

IV. TEVA'S GENERIC CELECOXIB WILL NOT INFRINGE ANY VAILD/ENFORCEABLE CLAIM OF THE '165 PATENT

A. Teva's Generic Celecoxib Will Not Infringe Claims 6-14 and 19-21 of the '165 Patent

Claims 6-14 and 19-21 of the '165 patent are limited to compositions containing a therapeutically-effective amount of an active compound selected from a group of compounds that does not include celecoxib. Teva's generic celecoxib products will not contain any active pharmaceutical ingredient other than celecoxib. Therefore, Teva's celecoxib products do not literally infringe claims 6-14 and 19-21 of the '165 patent. Teva's celecoxib products also would

not infringe these claims under the doctrine of equivalents for the same reasons as provided above with respect to claims 4-6, 10 and 12 of the '823 patent.

B. Claims 1 and 2 of the '165 Patent Are Anticipated Under 35 U.S.C. § 102(b) By Canadian Patent 1,130,808

The '808 patent discloses compounds that are within the genus of compounds claimed in claims 1 and 2 of the '165 patent. At least one species disclosed in the '808 patent, as well as a small genus of disclosed compounds, is contained in the genus claimed by claims 1 and 2 of the '165 patent. The disclosure of even *a single* species, not to say a small genus, in the prior art anticipates a later claim to a genus containing that species. *In re Gosteli,* F.2d 1008, 1010 (Fed. Cir. 1989), *citing In re Slater,* 276 F.2d 408, 411 (C.C.P.A. 1960). Thus, the genus of compounds claimed in claims 1 and 2 of the '165 patent are invalid as anticipated by the '808 patent.

C. At Least Claims 1-5 and 15-18 of the '165 Patent Are Invalid As Obvious Under 35 U.S.C. § 103

At least claims 1-5 and 15-18 of the '165 patent are invalid under 35 U.S.C. § 103 as obvious in view of the '808 patent, the El-Khawass article, the '305 patent, the '142 patent, and/or the '518 patent. For the same reasons as set forth above with respect to the '823 patent, no secondary considerations overcome the otherwise strong case of obviousness that exists in connection with these '165 patent claims.

D. Claims 1-5 and 15-18 of the '165 Patent, If Not Obvious, Are Invalid Under 35 U.S.C. § 112

Claims 1-5 and 15-18 of the '165 patent, if not obvious, and if construed to encompass virtually any pharmaceutical composition containing the recited substituted pyrazolyl benzenesulfonamides, are invalid under 35 U.S.C. § 112 for lack of adequate written description and for lack of enablement.

Independent claims 1 and 15 include the limitations that the claimed pharmaceutical composition comprises a "therapeutically-effective amount of a compound and a pharmaceutically-acceptable carrier or diluent." The remaining claims depend either directly or indirectly from claims 1 or 15, and therefore contain these same limitations. Therefore, should the claims be construed to encompass *any* pharmaceutical composition containing the compounds listed, in amounts in a possible range of 0.01 mg to over 2000 mg, they would be invalid for lack of adequate written description and for lack of enablement. The narrower preferred ranges disclosed do not remedy this lack of written description or enablement for the reasons set forth below.

Nothing in the '165 patent proves that the applicants were "in possession" of a pharmaceutical composition containing a therapeutically-effective amount of the subject compounds. In fact, the specification, prosecution history and other evidence suggest that the

applicants were *not* in possession of the alleged invention at the time the application was first filed. For example, the '165 patent does not explain how to achieve a "composition" containing a "therapeutically-effective" amount of the claimed compounds. The '165 specification contains no examples of any compositions illustrating a compound with a particular carrier, or showing that the amount of the compound, as a result of the composition, is, or would be, therapeutically effective. The '165 patent claims do not even specify the recipient of the composition.

The question of enablement under § 112, first paragraph, involves determining whether a patent disclosure would have enabled one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *Adang v. Fischhoff*, 286 F.3d 1346, 1355 (Fed. Cir. 2002), *citing Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *see also Glaxo Wellcome, Inc. v. Eon Labs Manufacturing, Inc.*, 2002 WL 1874830, *2 (S.D.N.Y. Aug. 13, 2002). The '165 specification provides no guidance as to how to achieve a composition containing a therapeutically-effective amount, and the claims are so broad as to also provide no guidance how to choose effective compositions within the broad ranges without complicated and laborious trial and error. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (A lack of enablement rejection under section 112, first paragraph, is appropriate where the specification fails to teach those in the art to make and use the invention as broadly as it is claimed without undue experimentation); *see In re Vaeck*, 947 F.2d 488, 495-96 (Fed. Cir. 1991).

Moreover, the claims of the '165 patent do not meet the requirements of § 112, first paragraph, because they do not recite: (1) a disease to be treated, (2) a rate of administration, (3) a numerical dosage range, (4) a dosage form or (5) a recipient of the composition. Similar pharmaceutical claims have been found to violate § 112. *See In re Gardner*, 427 F.2d 786 (C.C.P.A. 1970).

Lacking such specificity, the '165 claims may be analyzed as containing only functional limitations: the equivalent of a "means" clause, *i.e.*, a means (composition) for providing a therapeutically effective amount of a given compound. Claims containing only such means clauses may be invalid. *Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245, 256-57 (1928); *Electric Co. v. Wabash Appliance Co.*, 304 U.S. 364, 371 (1938). Even if valid, they may be limited to the means disclosed in the specification for achieving the desired ends, and the equivalents thereof. 35 U.S.C. § 112, sixth paragraph. Because the '165 patent claims cover all pharmaceutical compositions containing the subject compounds, without further guidance or direction in the specification for therapeutic administration, either the claims should be restricted to the scope of the embodiments disclosed in the specification, or the claims are impermissibly broad. In either case, the broad scope of the '165 patent claims is neither adequately described nor adequately enabled by the '165 patent as required by 35 U.S.C. § 112, first paragraph.

V. TEVA'S GENERIC CELECOXIB WILL NOT INFRINGE ANY VAILD/ENFORCEABLE CLAIM OF THE '068 PATENT

A. Teva's Generic Celecoxib Will Not Infringe Claims 5-10 of the '068 Patent

Claims 5-10 of the '068 patent are limited to methods of using compounds that do not include celecoxib. Teva's generic celecoxib products will not contain any active pharmaceutical ingredient other than celecoxib. Therefore, the use of Teva's celecoxib products would not literally infringe claims 5-10 of the '068 patent. Use of Teva's celecoxib products also would not infringe these claims under the doctrine of equivalents for the same reasons as provided above with respect to claims 4-6, 10 and 12 of the '823 patent.

B. Inequitable Conduct Renders All Claims of the '068 Patent Unenforceable

1. Prosecution of the '068 Patent and Related Art

Bulock prosecuted the '068 patent. The '068 patent was filed on September 6, 1996 as U.S. application Serial No. 648,113 ("the '113 application"), the U.S. national phase of PCT application No. PCT/US94/12720. This PCT application published as WO 95/15316 on June 8, 1995 ("the '316 PCT application"). The '316 PCT application contained 8 claims directed to certain compounds and the use of those compounds for treating inflammation and inflammation-associated disorders. The '316 PCT application included as new matter, *inter alia*, many new compounds and new disclosures with respect to COX-2 and inflammation. In addition, the new disclosure included a statement that the compounds of Formula I would be useful for "the prevention of colorectal cancer." Beyond that statement, there is no mention of the use of COX-2 inhibitors for the treatment or prevention of colorectal cancer, or other types of neoplasias, in the '316 PCT application.

During prosecution of the '068 patent, Bulock held an interview with the Examiner on April 7, 1997. In the Interview Summary, the Examiner stated:

> Method claims limited to the use of the compounds of the allowed parent cases are to be presented. An article demonstrating the relation of COX II activity to colorectal cancer prevention is to be supplied. Colorectal cancer prevention is to be inserted into claim 23.

We conclude that the article referred to by the Examiner is Bandaru S. Reddy *et al.*, *Evaluation of Cyclooxygenase-2 Inhibitor for Potential Chemopreventative Properties in Colon Carcinogenesis*, Cancer Research, 56, pp. 4566-4569 (1996) (the "Reddy publication."). This article, not otherwise mentioned in the file history, is identified on the face of the '068 patent.

The Reddy publication evaluated celecoxib as a selective COX-2 inhibitor for potential chemopreventive activity against colonic aberrant crypt foci ("ACF") formation. Reddy publication, at 4568. ACF are putative preneoplastic lesions, and their presence or absence can be used to predict the outcome of colon tumors. *Id.* The study found that celecoxib inhibited

colonic ACF formation and crypt multiplicity. *Id.* This "finding was significant because [celecoxib], through its ability to inhibit COX-2 expression, has *the potential to block the development and/or progression of colon carcinogenisis.*" *Id.* (emphasis added). The Reddy publication was received on July 19, 1996, accepted for publication on August 29, 1996, and published in the October 15, 1996 issue of Cancer Research. Its co-authors were Bandaru S. Reddy ("Reddy"), Chinthalapally V. Rao ("Rao") and Karen Siebert ("Siebert").

None of the Reddy publication authors are listed as inventors on the '068 patent. Reddy was the first listed author of the publication, indicating that he was the principal researcher or designer of the studies described therein. Indeed, the references cited in the Reddy publication reveal that Reddy had been involved in colon cancer research since at least 1986. *Id.*, 4569, ref. 2. The Reddy publication also reveals that Reddy and Rao were associated with the American Health Foundation's Division of Nutritional Carcinogenesis, which provided the major funding for the study. *Id.*, at 4566. Siebert, on the other hand, was associated with Searle Research and Development, which "[s]upported [the study] in part." *Id.*

Following the April 7, 1997 Examiner interview described above, Bulock filed a Supplemental Amendment canceling claims 1-14 and 21-22, amending claims 16-17 and adding claims 23-36. New claim 23 was directed to "a method of treating inflammation or an inflammation associated disorder" comprising administration of a therapeutically effective amount of a compound chosen from a large genus of compounds (the same genus as set forth in claim 1). Claim 36 was as follows:

> 36. The method of Claim 23, for use in the prevention of colorectal cancer.

The April 15, 1997 Notice of Allowability stated: "In claim 23, line 2 following 'disorder' insert --or a method for the prevention of colorectal cancer--."

On September 29, 1997, the Applicants filed Supplemental Amendment and Petition to Amend Before Patent Issuance to remove subject matter allowed in U.S. Patent No. 5,521,207. This petition was granted on March 12, 1998 and a second Notice of Allowability sent. The '068 patent issued on June 2, 1998.

2. U.S. Patent No. 5,972,986 ("The '986 Patent")

The '986 patent, entitled "Method of Using Cyclooxygenase-2 Inhibitors in the Treatment and Prevention of Neoplasia," was filed on October 14, 1997 as application Serial No. 08/949,922 ("the '922 application"). The '986 patent is assigned to G.D. Searle & Co. The '986 patent was filed while the '113 application (which issued as the '068 patent) was still pending at the PTO. On its face, the '968 patent identifies three inventors: Karen Seibert, Jaime Masferrer and Gary B. Gordon. None of these inventors, however, are identified as inventors on the face of the '068 patent.

Similar to claim 18 of the '068 patent[2], the claims of the '986 patent are directed to methods of treating neoplasias by using a class of COX-2 inhibitors. The neoplasias considered within the scope of the '986 patent vary widely, from brain and bone cancers to esophogeal and liver cancers, and include colon and colorectal cancers. *Id.*, col. 2, lines 45-50. At the time of the '986 patent application, COX-2 inhibitors were known to prevent the production of prostaglandins by COX-2. *Id.*, col. 1, lines 27-35. According to the '986 patent, the presence of COX-2 has been observed in neoplastic disease. *Id.*, lines 55-58. In this context, the '986 patent discloses preventing a neoplasia that produces prostaglandin by inhibiting COX-2 and claims a class of compounds disclosed in the '068 patent, which includes celecoxib, to be used for treating neoplasia. *Id.*, col. 9, lines 1-4.

Despite having cited the '316 PCT application as a reference, which discusses the use of celecoxib for the treatment of colorectal cancer, the '986 patent asserts that the use of COX-2 inhibitors "for treating colon cancer or for treating or preventing other neoplasias has not been previously described." *Id.*, col. 1, lines 63-65. This statement is false in view of the fact that the '316 PCT application (the '068 patent) specifically describes the use of COX-2 inhibitors for preventing colorectal cancer – a type of epithelial carcinoma also disclosed in the '986 patent as colorectal cancer. Bulock, who was prosecuting both the '068 and '986 patent, knew or should have known that this statement was false. Bulock's prosecution of both the '068 and '986 patents should have also alerted Bulock to a possible inventorship issue, as the '068 and '986 patents had claims directed to the same subject matter, but did not have overlapping inventors.

3. Searle's Inequitable Conduct Renders The '068 Patent Unenforceable

Facts and circumstances surrounding the prosecution of the '068 patent demonstrate that Searle intentionally breached its duty of candor under 37 C.F.R. § 1.56 by omitting the names of the authors of the Reddy publication as inventors of the '068 patent, which claims treatment or prevention of colorectal cancer with COX-2 inhibitors. This omission deprived the Patent Office of the opportunity to assess whether there was an inventorship problem with respect to the '068 patent. This omission also allowed Searle to avoid naming two third-parties, Reddy and Rao, as inventors with respect to the '068 and '986 patents. Due to Searle's inequitable conduct, the '068 patent is unenforceable.

a. Searle Breached Its Duty of Candor Under 37 C.F.R. § 1.56

The '986 patent was filed on October 14, 1997 and the '068 patent did not issue until June 2, 1998, thus the patent applications for these two patents were copending. Under 37 C.F.R. § 1.56, Bulock had a duty to inform the Examiner of any copending United States patent application material to patentability of the '068 patent. *MPEP* § 2001.06(b). The '986 patent was material to the prosecution of the '068 patent because the claims of the '986 patent cover the same subject matter as that claimed in the '068 patent.

---

[2] Claim 18 of the '068 patent states: "The method of claim 1 for use in prevention of colorectal cancer."

Because the '068 and '986 patents have overlapping subject matter and certain claims that claim the same invention,[3] the '986 patent application was material to prosecution of the '086 patent. Questions of inventorship under 102(f) also exist, because only the true inventor of these claims can receive a patent, yet different inventive entities are identified on the face of the '068 and '986 patents. A reasonable Examiner would therefore have considered it important to know about the '986 patent application before allowing the '068 patent to issue. Hence, the '986 patent application was material to prosecution of the '068 patent and Bulock should have disclosed it to the Examiner of the '068 patent. Bulock's failure to do so constituted a breach of his duty under 37 C.F.R. § 1.56.

b. Searle Had an Intent to Deceive

Searle's intent to deceive can be inferred from the facts and circumstances surrounding Bulock's conduct. *Molins*, 48 F.3d 1172 at 1180-81. Here, at least the following facts establish a strong inference of Searle's intent to deceive.

First, Bulock copied text from the '068 patent family into the '986 application. Portions of the '068 and '986 patent applications are very similar. For instance, the first paragraph of the "BACKGROUND OF THE INVENTION" sections are identical.[4] Likewise, with the exception of the first word, the second paragraph of this section is also identical. This suggests that the invention of the '986 patent was related to the invention of the '068 patent. Yet Bulock did not take advantage of the '068 patent's priority date, instead filing a new application.

Second, Bulock prosecuted claims in the '986 patent that had the same scope as claims he prosecuted in the '068 patent. As stated above, the claims of the '986 patent as originally filed claimed the same subject matter as those of the '068 patent.

Third, Bulock considered claim overlap during prosecution of the '068 patent. For example, at the end of September 1997, just two weeks before Bulock filed the '986 patent application, Bulock filed a Supplemental Amendment to remove claims covered by U.S. Patent No. 5,521,207. The accompanying petition stated that "[t]he Claims [of the '068 patent] were recently compared with those of U.S. Patent No. 5,521,2[0]7 and overlap was discovered." Yet, Bulock still filed the '986 patent application with claims that overlapped in scope with those being prosecuted in the '068 patent.

Fourth, Bulock prosecuted the '068 patent and knew about the Reddy publication and its importance to the Examiner during prosecution of the '068 patent. Bulock's filing of the '986 patent only one day before the one-year bar date based on the Reddy reference evidences Bulock's intent to avoid the Reddy reference as prior art under 35 U.S.C. § 102(b). This indicates that the subject matter disclosed in the Reddy reference, *i.e.*, the effect of COX-2 on treating colorectal cancer, was material to '986 patent, and would also be material to the '068

[3] As filed, claim 7 of the '986 patent claimed the same invention as claim 18 of the '068 patent.

[4] This section is also identical in the '823 patent, from which the '068 patent claims priority.

patent. It further indicates that the authors of the Reddy reference were material for purposes of assessing inventorship of the '068 patent and '986 patents.

Bulock was concerned about the prior art status of the Reddy publication because he believed that the Reddy article disclosed the invention of the '986 patent, which it does. The Reddy publication teaches the use of celecoxib to "block the development and/or progression of colon carcinogenesis." Moreover, Bulock used the Reddy publication to support the utility of claims in the '068 patent directed to the prevention of colorectal cancer. Filing claims in the '986 patent application for the treatment of colon cancer and for prevention or treatment of gastrointestinal cancer, just before the Reddy publication became a statutory bar against such claims, evidences Bulock's bad faith in filing the '986 patent application and failing to disclose its filing to the Examiner during prosecution of the '068 patent.

Bulock's filing of claims in the '986 patent application that covered the same scope as that of the '068 patent application -- use of compounds like celecoxib for preventing or treating colorectal cancer -- raises inventorship issues that Bulock had a duty to investigate. *See, Brasseler*, 267 F.3d at 1383. Bulock endeavored to avoid this duty by withholding the '986 patent application from the Examiner of the '068 patent. This behavior evidences Bulock's intent to deceive the PTO. *Id.*

c. Searle Engaged In Inequitable Conduct

Given that the '986 patent application was strongly material, the level of intent that needs to be shown can be proportionally less. *Brasseler*, 267 F.3d at 1381. Viewing the "evidence as a whole" indicates that Bulock: (a) knew that the '986 patent covered the same subject matter, and indeed the same scope, as the '068 patent; (b) did not identify Reddy and Rao (non Searle employees) as inventors; and (c) did not disclose to the Examiner the '986 patent application despite its materiality, thereby avoiding questions of inventorship and potential loss of the earlier priority date of the '068 patent application. Thus, Bulock's actions (and inactions) evidence intent to deceive the Examiner of the '068 patent application.

Based on the foregoing, Searle engaged in inequitable conduct rendering the '068 patent unenforceable.

VI. CONCLUSION

For the foregoing reasons, all claims of U.S. Patent Nos. 5,466,823, 5,563,165 and 5,760,068 are invalid or unenforceable, or would not be infringed, either literally or under the doctrine of equivalents, by the manufacture, use or sale of Teva's celecoxib products. Teva reserves the right to develop additional grounds, reasons or authorities that any or all of the claims of these U.S. patents are invalid, unenforceable or not infringed.